ATGCCCTGCGTGCAAGCCCAGTATAGCCCTTCACCTCCGGGGTCCACTTACGCCACGCAG
ACTTATGGCTCGGAATACACCACAGAAATCATGAACCCCGACTACACCAAGCTGACCATG
GACCTCGGTAGCACGGGGATCATGGCCACCGCCACTACATCCCTGCCCAGCTTCAGTACC
TTCATGGAGGGCTACCCCAGCAGCTGCGAACTCAAGCCCTCCTGCCTGTACCAAATGCCG
CCTTCTGGGCCTCGGCCTTTGATCAAGATGGAAGAGGGTCGCGAGCATGGCTACCACCAC
CACCATCACCATCACCATCATCACCACCACCACCAGCAACAGCAGCCGTCCATTCCTCCT
CCCTCCGGCCCCGAGGACGAGGTACTGCCCAGCACCTCCATGTACTTCAAGCAGTCTCCG
CCGTCTACACCGACCACTCCAGGCTTCCCCCCGCAGGCGGGGGCGCTGTGGGACGACGAG
CTGCCCTCTGCGCCTGGCTGCATCGCTCCGGGACCGCTGCTGGACCCGCAGATGAAGGCG
GTACCCCCCATGGCCGCTGCTGCGCGCTTCCCGATCTTCTTCAAGCCCTCACCGCCACAC
CCTCCCGCGCCCAGTCCAGCCGGCGGCCACCACCTCGGCTATGACCCCACGGCCGCAGCT
GCACTCAGTCTGCCCCTGGGAGCCGCGGCCGCAGCAGGCAGCCAAGCTGCTGCGCTCGAG
GGCCACCCATACGGGCTCCCGCTGGCCAAGAGGACGGCCACGCTGACCTTCCCTCCGCTG
GGCCTCACAGCCTCCCCCACCGCGTCCAGCCTGCTGGGAGAGAGCCCCAGCCTCCCATCG
CCACCCAATAGGAGCTCATCATCTGGGGAAGGCACATGTGCCGTGTGCGGCGACAACGCT
GCCTGCCAGCACTACGGAGTCCGCACCTGCGAGGGCTGCAAGGGCTTCTTCAAGAGAACG
GTGCAGAAAAATGCAAAATATGTTTGCCTGGCAAATAAAAACTGCCCAGTGGACAAGAGA
CGCCGAAACCGATGTCAGTACTGCAGATTTCAGAAGTGTCTCAGTGTCGGGATGGTTAAG
GAAGTTGTGCGTACAGACAGTCTGAAAGGGAGGAGAGGTCGTCTGCCTTCCAAACCAAAG
AGCCCACTACAACAGGAGCCCTCGCAGCCCTCCCCGCCATCTCCTCCGATCTGTATGATG
AATGCCCTTGTCCGAGCTTTAACAGATGCAACACCCAGAGATCTTGATTATTCCAGATAC
TGTCCCACCGACCAGGCCACTGCAGGCACAGATGCTGAGCACGTGCAACAGTTCTACAAC
CTTCTGACGGCCTCCATTGACGTGTCCAGAAGCTGGGCAGAAAAGATCCCAGGATTCACT
GATCTCCCCAAAGAAGATCAGACGTTACTTATAGAATCAGCCTTTTTGGAGCTGTTTGTT
CTTAGACTTTCCATCAGGTCAAACACTGCTGAAGATAAGTTTGTGTTCTGCAATGGACTT
GTCCTGCATCGACTTCAGTGCCTTCGAGGATTTGGGGAGTGGCTCGACTCCATTAAAGAC
TTTTCTTTAAACTTGCAGAGCCTGAACCTTGATATCCAAGCCTTAGCCTGCCTGTCAGCA
CTGAGTATGATCACAGAGCGACATGGGTTAAAAGAACCAAAGAGAGTGGAGGAGCTATGC
ACCAAGATCACAAGCAGCTTAAAGGACCACCAGAGGAAGGGACAGGCTCTGGAGCCCTCG
GAGCCTAAGGTCCTGCGCGCGCTGGTAGAACTGAGAAAGATCTGTACCCAGGGCCTCCAG
CGCATCTTCTACCTGAAGCTAGAGGACTTGGTACCTCCACCTTCTGTCATCGACAAGCTC
TTCCTTGACACCCTGCCTTTCTGA (SEQ ID NO:1)

MPCVQAQYSPSPPGSTYATQTYGSEYTTEIMNPDYTKLTMDLGS
TGIMATATTSLPSFSTFMEGYPSSCELKPSCLYQMPPSGPRPLIKMEEGREHGYHHHH
HHHHHHHHHQQQQPSIPPPSGPEDEVLPSTSMYFKQSPPSTPTTPGFPPQAGALWDDE
LPSAPGCIAPGPLLDPQMKAVPPMAAAARFPIFFKPSPPHPPAPSPAGGHHLGYDPTA
AAALSLPLGAAAAAGSQAAALEGHPYGLPLAKRTATLTFPPLGLTASPTASSLLGESP
SLPSPPNRSSSSGEGTCAVCGDNAACQHYGVRTCEGCKGFFKRTVQKNAKYVCLANKN
CPVDKRRRNRCQYCRFQKCLSVGMVKEVVRTDSLKGRRGRLPSKPKSPLQQEPSQPSP
PSPPICMMNALVRALTDATPRDLDYSRYCPTDQATAGTDAEHVQQFYNLLTASIDVSR
SWAEKIPGFTDLPKEDQTLLIESAFLELFVLRLSIRSNTAEDKFVFCNGLVLHRLQCL
RGFGEWLDSIKDFSLNLQSLNLDIQALACLSALSMITERHGLKEPKRVEELCTKITSS
LKDHQRKGQALEPSEPKVLRALVELRKICTQGLQRIFYLKLEDLVPPPSVIDKLFLDT
LPF (SEQ ID NO:2)

FIGURE 1

```
   1 ccgagtctcc tgcctcccgc cccccacccc tccagcgcct gctcctcctc cgctccccat
  61 acacagacac gctcacaccc gctccttcac ttgcacacac agacacacgc gcgctcacac
 121 gctccgcaca cacactccac tctctcccgc gcgctcacac ccctctctct cggcgccctc
 181 gccggtgtcg cgccgcgccg cgccgcagcc ggacgccccc ccagggctca ctttgcaacg
 241 ctgacagagc gggcagtggc cgtggaggtg ggaaacgtgg cgacatccta gcccctggtc
 301 gcagccggag actggacgct gcggaacctc tcggcggcgc tctcccatga gttgggatcg
 361 cagcatcccc agccagccgc tgctcaccgc ctctgggagc cgctgggttt gtgcaccgca
 421 gcccttccgg gacagcagct gtgactctcc cccaatccag atttcggggt cgctctctag
 481 aaactcgctc taaagacgga acctccacag aacccaaagc ccactgcggg agagcgcagc
 541 ccgacaagcc cgggcgctga gcctggaccc tcaacagagc gggccagcac agcggcggcg
 601 gctgcttcgc ctatcccgac gtccccgcct cctacactct cagcctccgc tggagagacc
 661 cccagcccca ccattcagcg cgcaagatac cctccagata tgccctgcgt gcaagcccaa
 721 tatagccctt cgcctccggg gtccacttat gccacgcaga cttatggctc ggaatacacc
 781 acagaaatca tgaaccccga ctatgccaag ctgaccatgg acctcggtag cacggggatc
 841 atggccacgg ccacgacgtc cctgcccagc ttcagtacct tcatggaggg ctaccccagc
 901 agctgcgaac tcaagccctc ctgcctgtac caaatgccgc cttctgggcc tcggcctttg
 961 atcaagatgg aagagggtcg cgagcatggc taccaccacc accaccacca tcaccatcat
1021 catcaccacc accaccagca gcagcagccg tccattcctc ctccctctgg ccccgaggac
1081 gaggtactgc ccagcacctc catgtacttc aagcagtctc cgccgtctac gccgaccact
1141 ccaggcttcc ccccgcaggc gggggcgctg tgggacgacg agctgccctc tgcgcctggc
1201 tgcatcgctc cgggaccgct gctggacccg cagatgaagg cagtgccccc aatggccgct
1261 gctgcgcgct tcccgatctt cttcaagccc tcaccgccac accctcccgc gcccagccca
1321 gccggcggcc accacctggg ctatgacccc acggccgcag ctgcgctcag tctacccctg
1381 ggagccgcgg ccgccgcggg cagccaagct gctgcgctcg agggccatcc gtacgggctc
1441 ccgctggcca agaggacggc cacgttgacc ttccctccgc tgggcctcac agcgtcccct
1501 accgcgtcca gcctgctggg agagagcccc agcctaccat cgccacccaa taggagctca
1561 tcatccggcg agggcacgtg tgctgtgtgc ggggacaatg ctgcctgcca gcactacgga
1621 gtccgcacct gcgagggctg caagggcttc ttcaagagaa cggtgcagaa aaacgcaaaa
1681 tatgtttgct tggcaaataa aaactgcccg gtagacaaga gacgtcgaaa tcgatgtcag
1741 tactgcaggt ttcagaagtg tctcagtgtc gggatggtga aggaagttgt gcgtacagat
1801 agtctgaaag ggaggagagg tcgtctgcct tccaaaccaa agagcccact acaacaggag
1861 ccctcgcagc cctccccacc atctcctccg atctgtatga tgaacgccct tgtccgagct
1921 ttaacagacg caacgcccag agaccttgat tactccagat actgtcccac cgaccaggcc
1981 actgcgggca cagacgctga gcacgtgcag cagttctaca accttctgac ggcctccatc
2041 gacgtgtcca gaagctgggc agaaaagatc cccggattca ctgatctccc caaagaagat
2101 cagacgttac ttatagaatc agccttttg gagctgttcg ttcttagact ttctatcagg
2161 tcaaacactg ctgaagataa gtttgtgttc tgcaatggac ttgtcctgca ccgacttcag
2221 tgccttcgcg gatttgggga gtggctcgac tccattaaag acttttcttt aaatttgcag
2281 agcctgaacc ttgatatcca agccttagcc tgcctgtcag cactgagtat gatcacagag
2341 cgacatgggt taaaagaacc aaagagagtg gaggagctat gcaacaagat cacaagcagc
2401 ttaaaggacc accagaggaa gggacaggct ctggagccct cagagcccaa ggtccttcgc
2461 gcactggtgg aactgaggaa gatctgcacc cagggcctcc agcgtatctt ctacctgaag
2521 ctggaggact tggtgtcccc accttctgtc atcgacaagc tcttccttga taccctgcct
2581 ttctgagcag gggaagcctg agcagagagc tacttgctct gctggcactg gtcattaagt
2641 gagcaaaagg atgggtttga acacctgccc ctctatcctt cctccagggg aaaaagcagc
2701 tcccatagaa agcaaagact ttttttttc ctggcacctt tccttacaac ctaaagccag
2761 aaaccttgca gagtattgtg ttggggttgt gttttatatt taggctttgg tgggtgggct
2821 gggaggggt aaaatagttc atgaggcttt tctaagaaat tgctgacgaa gcacttttgg
2881 atgatgctat cccagcagtg gggtggggag aaaggataat ataactgttt taaaaactct
2941 ttccgggga atatgactat ggttgctttg tatttaaaaa taagaacagc caagggctgt
3001 tttaccaggg tagggctgtg tcttaagact gatcccttta gtatgtactt cccggatcga
3061 ggcacataag tggtgcaaat gaggcgggga aattcttcat ttcttcattt ctttcttctt
3121 cttaaaataa aatggcaaaa aaaaaaagat ggaagattat ctacaaatca gacttagcaa
```

FIGURE 2A

```
3181 aatgataatg gctattcgct tccacataca agtgcaattt tttagagtgc tgtcttacta
3241 agtcttgttt gtgaactctc cctcatttta tatgaaaata agaaggaggc agtcatgtta
3301 tcaaacggcg tgctcatttt cctagctcac ccttggtcca cctgccctgt agaacccttc
3361 ggaggtatgg cccttctaag actttcaggc cactcttgat ggaattcgac acccctcccc
3421 tcaacccatg actatccaga tgtcctgaat ggggatcagg ttataaaatg gattgcatat
3481 gactgtgttc gctgtgtgtt tgtcaacctg gacagagttc tctaaacctt ctttagttgt
3541 agcaagttcc tgattcctcc attcagaagc ccaaggagca ttgggtgact cgatcaaggg
3601 ttaaccctag gagaacatgc aaataagtag gaactgggtc agacagggta agcaccagag
3661 atgataagga tttatatata aatatatata aaattaattt ttgttattgg ttatagacaa
3721 ttttggaaag caagagaatc atctcttttt ttttttaaa gaggaaaaga tagtattgat
3781 gtattagcaa agattagtgg ggtacggttc aacattccgt gtttgtgccc ccttttctat
3841 gtttctactg ttgatggcat attattatga aatgattcgt tgcatagtgt ccttatttgt
3901 atgaacattt gtatgcacgt tctattgtaa tcgctttgcc tgtatttatt gcaagaccac
3961 cagctcctgg aggctgagtt acagaataat caaatggggt gttcgtggtg acttggatac
4021 accggttaga aattaaataa gcatatatat atatataaaa acatagcagg ttacatatat
4081 atttataatg tgtcttttta ttaaccattt gtacaataaa tgtcacttcc cacgcagtta
4141 ttttatcctt tgtttgcagt gacctttaag gcagcactgt ttagcacttt gatatgaaat
4201 tttttgctta tttttttgct aaattcaaat aacgtttgaa gatttttagg tctaaaagtc
4261 tttatattat atacactgta tcaagtcaag ataccttttgg ccgttttgct aagactcaaa
4321 ctttgaatgt caaaccaatg tcacggtagc ttctgttagc ttttaatcat ttttgcttta
4381 gtctttttttt ttaaaaaaaa (SEQ ID NO:3)
```

```
MPCVQAQYSPSPPGSTYATQTYGSEYTTEIMNPDYAKLTMDLGSTGIMATATTSLPSFSTFMEGYPSSCELKPSCLYQMPPSGPRP
LIKMEEGREHGYHHHHHHHHHHHHHHQQQQPSIPPPSGPEDEVLPSTSMYFKQSPPSTPTTPGFPPQAGALWDDELPSAPGCIAPG
PLLDPQMKAVPPMAAAARFPIFFKPSPPHPPAPSPAGGHHLGYDPTAAAALSLPLGAAAAAGSQAAALEGHPYGLPLAKRTATLTF
PPLGLTASPTASSLLGESPSLPSPPNRSSSSGEGTCAVCGDNAACQHYGVRTCEGCKGFFKRTVQKNAKYVCLANKNCPVDKRRRN
RCQYCRFQKCLSVGMVKEVVRTDSLKGRRGRLPSKPKSPLQQEPSQPSPPSPPICMMNALVRALTDATPRDLDYSRYCPTDQATAG
TDAEHVQQFYNLLTASIDVSRSWAEKIPGFTDLPKEDQTLLIESAFLELFVLRLSIRSNTAEDKFVFCNGLVLHRLQCLRGFGEWL
DSIKDFSLNLQSLNLDIQALACLSALSMITERHGLKEPKRVEELCNKITSSLKDHQRKGQALEPSEPKVLRALVELRKICTQGLQR
IFYLKLEDLVSPPSVIDKLFLDTLPF (SEQ ID NO:4)
```

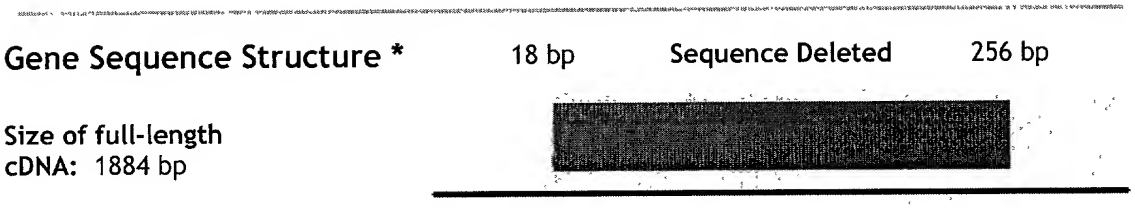
FIGURE 2B

underlined = deleted in targeting construct

[ ] = sequence flanking Neo insert in targeting construct

[ATGCCCTGCGTGCAAGC] CCAGTATAGCCCTTCACCTCCGGGGTCCACTTACGCCACGCAG
ACTTATGGCTCGGAATACACCACAGAAATCATGAACCCCGACTACACCAAGCTGACCATG
GACCTCGGTAGCACGGGGATCATGGCCACCGCCACTACATCCCTGCCCAGCTTCAGTACC
TTCATGGAGGGCTACCCCAGCAGCTGCGAACTCAAGCCCTCCTGCCTGTACCAAATGCCG
CCTTCTGGGCCTCGGC [CTTTGATCAAGATGGAAGAGGGTCGCGAGCATGGCTACCACCAC
CACCATCACCATCACCATCATCACCACCACCACCAGCAACAGCAGCCGTCCATTCCTCCT
CCCTCCGGCCCCGAGGACGAGGTACTGCCCAGCACCTCCATGTACTTCAAGCAGTCTCCG
CCGTCTACACCGACCACTCCAGGCTTCCCCCCGCAGGCGGGGGCGCTGTGGGACGACGAG
CTGCCCTCTGCGCCTGGCTGCATCGCTCCGGGACCGCTGCTGGACCCGCAGATGAAGGCG
GTACCCCCCATGGCCGCTGCTGCGCGCTTCCCGATCTT] CTTCAAGCCCTCACCGCCACAC
CCTCCCGCGCCCAGTCCAGCCGGCGGCCACCACCTCGGCTATGACCCCACGGCCGCAGCT
GCACTCAGTCTGCCCCTGGGAGCCGCGGCCGCAGCAGGCAGCCAAGCTGCTGCGCTCGAG
GGCCACCCATACGGGCTCCCGCTGGCCAAGAGGACGGCCACGCTGACCTTCCCTCCGCTG
GGCCTCACAGCCTCCCCCACCGCGTCCAGCCTGCTGGGAGAGAGCCCCAGCCTCCCATCG
CCACCCAATAGGAGCTCATCATCTGGGGAAGGCACATGTGCCGTGTGCGGCGACAACGCT
GCCTGCCAGCACTACGGAGTCCGCACCTGCGAGGGCTGCAAGGGCTTCTTCAAGAGAACG
GTGCAGAAAAATGCAAAATATGTTTGCCTGGCAAATAAAAACTGCCCAGTGGACAAGAGA
CGCCGAAACCGATGTCAGTACTGCAGATTTCAGAAGTGTCTCAGTGTCGGGATGGTTAAG
GAAGTTGTGCGTACAGACAGTCTGAAAGGGAGGAGAGGTCGTCTGCCTTCCAAACCAAAG
AGCCCACTACAACAGGAGCCCTCGCAGCCCTCCCCGCCATCTCCTCCGATCTGTATGATG
AATGCCCTTGTCCGAGCTTTAACAGATGCAACACCCAGAGATCTTGATTATTCCAGATAC
TGTCCCACCGACCAGGCCACTGCAGGCACAGATGCTGAGCACGTGCAACAGTTCTACAAC
CTTCTGACGGCCTCCATTGACGTGTCCAGAAGCTGGGCAGAAAAGATCCCAGGATTCACT
GATCTCCCCAAAGAAGATCAGACGTTACTTATAGAATCAGCCTTTTTGGAGCTGTTTGTT
CTTAGACTTTCCATCAGGTCAAACACTGCTGAAGATAAGTTTGTGTTCTGCAATGGACTT
GTCCTGCATCGACTTCAGTGCCTTCGAGGATTTGGGGAGTGGCTCGACTCCATTAAAGAC
TTTTCTTTAAACTTGCAGAGCCTGAACCTTGATATCCAAGCCTTAGCCTGCCTGTCAGCA
CTGAGTATGATCACAGAGCGACATGGGTTAAAAGAACCAAAGAGAGTGGAGGAGCTATGC
ACCAAGATCACAAGCAGCTTAAAGGACCACCAGAGGAAGGGACAGGCTCTGGAGCCCTCG
GAGCCTAAGGTCCTGCGCGCGCTGGTAGAACTGAGAAAGATCTGTACCCAGGGCCTCCAG
CGCATCTTCTACCTGAAGCTAGAGGACTTGGTACCTCCACCTTCTGTCATCGACAAGCTC
TTCCTTGACACCCTGCCTTTCTGA

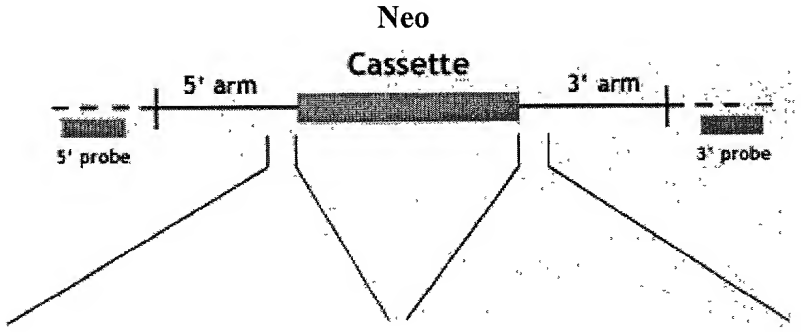
FIGURE 3A



Targeting Vector*
(genomic sequence)

Construct Number: 4512

Arm Length:
5': 2.7 kb
3': 3 kb



Targeting Vector
Endogenous Locus

* Not drawn to scale

5'>CCCTTTGACAGTCAGGAACTC AGCTGTCTTCCCAGCCAGGAAGAA AGTAAGCTAGGAGCATTCAGTCTT TGCCAGCAGGTGGGAGAGGATACC ACTTTCTTGTTTCCTGATTCAAGA GCAGTGGAACCAGCTGCAGATGGA GTGTCAACTGGCTTCTGAGCCCTT TTCTCTGTCCCTCCAGATATGCCC TGCGTGCAAGC<3' (SEQ ID NO:5)	5'>CTTTGATCAAGATGGAAGAGG ATCGCGAGCATGGCTACCACCACC ACCATCACCATCACCATCATCACC ACCACCACCAGCAACAGCAGCCGT CCATTCCTCCTCCCTCCGGCCCCG AGGACGAGGTACTGCCCAGCACCT CCATGTACTTCAAGCAGTCTCCGC CGTCTACACCGACCACCCCAGGCT TCCCCCCGCAG<3' (SEQ ID NO:6)

PCT/US2005/046094

FIGURE 3B

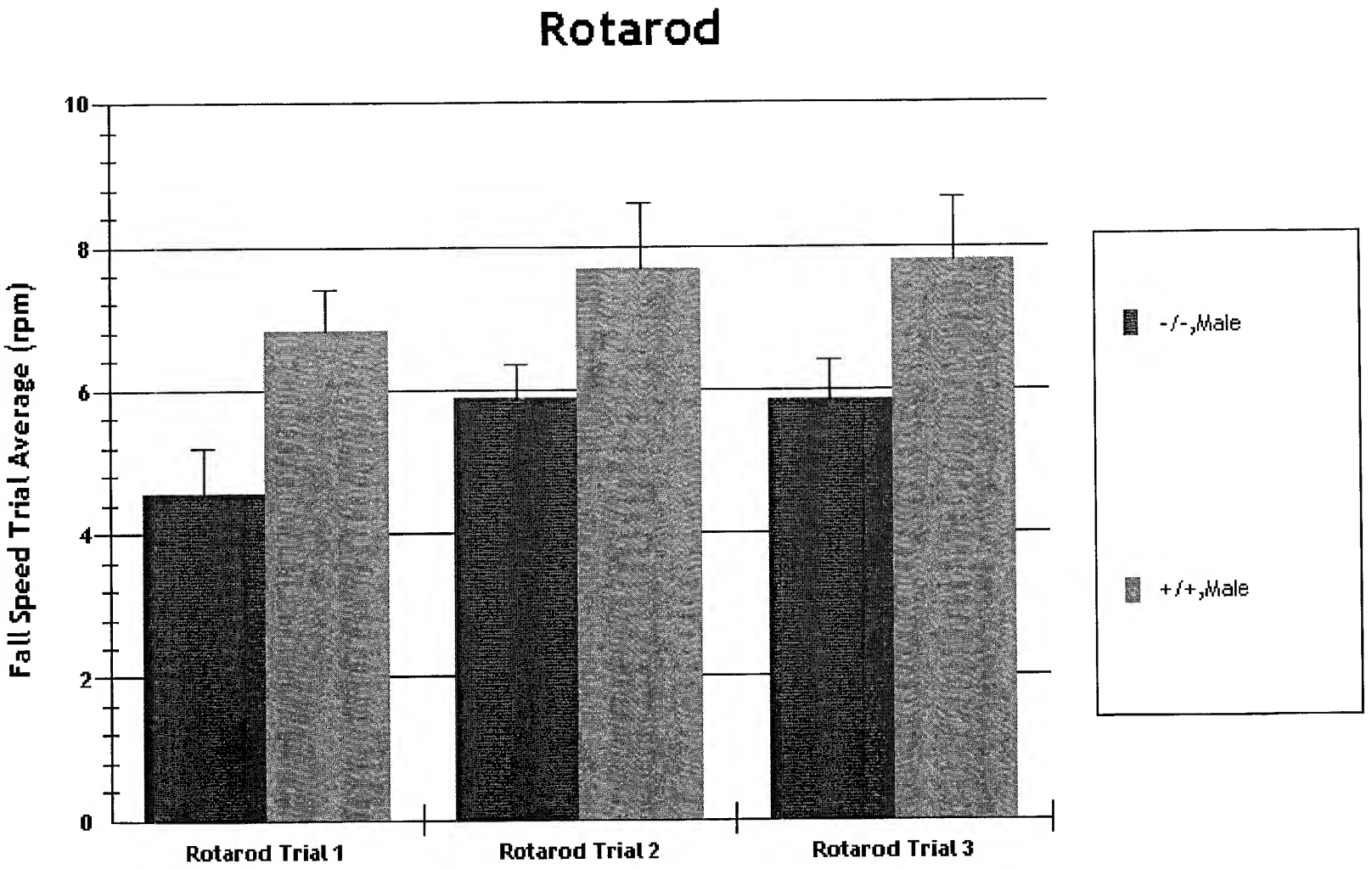

Rotarod
Fall Speed Trial Average (rpm)
10
8
6
4
2
0
Rotarod Trial 1
Rotarod Trial 2
Rotarod Trial 3
-/-,Male
+/+,Male

FIGURE 4

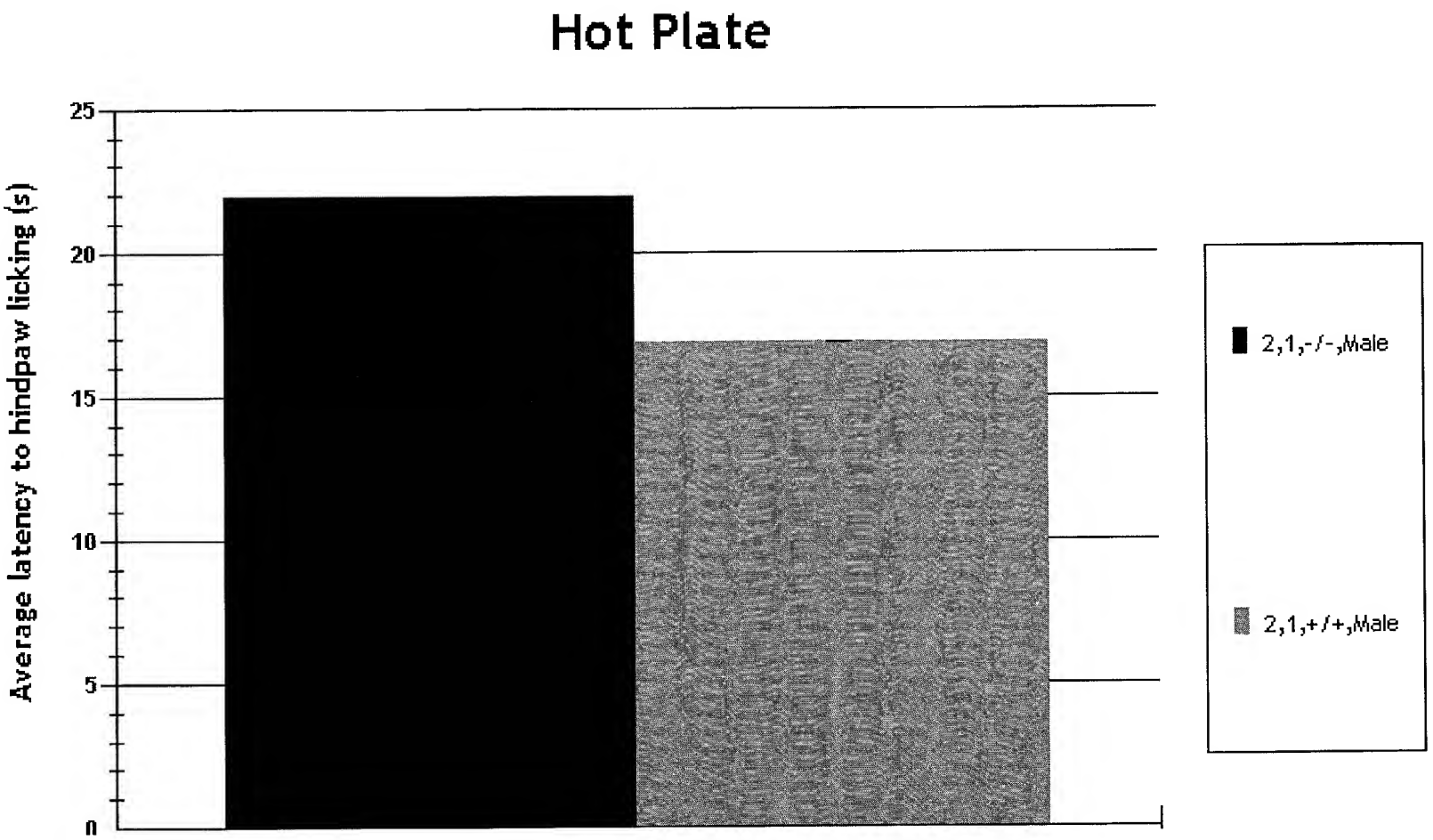

Hot Plate
Average latency to hindpaw licking (s)
25
20
15
10
5
0
2,1,-/-,Male
2,1,+/+,Male

FIGURE 5